Determining the Site of Brain Tumors

The Use of Radioactive Iodine and Phosphorus

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• By tests using radioactive iodine combined with diiodofluorescein, the site of tumors was correctly determined in 61 per cent of 39 cases of tumors of the cerebral hemispheres. In 19 cases where the focal radioactivity was increased 24 per cent or more over that of the surrounding area, there were no errors in localization. Fifteen patients with expanding intracranial lesions were tested at operation with radioactive phosphorus and 14 lesions were correctly localized. This procedure in which the needle probe was used was found of great value in rapidly locating and outlining the area of involvement.

RADIOACTIVE ISOTOPES of various elements are being used with increasing frequency to determine the site of brain tumors. There is still a difference of opinion regarding the accuracy of the results achieved, but in certain cases tests with radioisotopes appear to be of value. One of the most attractive features of these tests is that they are not harmful to the patient and the cost is not prohibitive. Various ions are selectively taken up by most brain tumors, and when these ions are radioactive their presence can be detected by radiation-sensitive counters. The type of radiation found useful in some circumstances may not be useful in others. For example gamma radiation, such as is given off by radioactive iodine, is able to penetrate the intact skull and is used to help determine the site of the lesion before the bone flap is turned at operation. After the skull is opened, beta rays, which are emitted by radioactive phosphorus, are the type found to be of value for precise determination of the location of the tumor. These travel only a few millimeters and are not picked up at a distance from the source. Thus the sensitive elements of the recording device must be in, or almost in, the substance of the tumor to pick up the rays.

The original work on the use of radioisotopes to determine the site of brain tumors was done by Moore and associates at the University of Minnesota in 1947.[5] Radioactive iodine combined with diiodofluorescein was used, but in this combination the radioactivity was soon lost, the dye being rapidly excreted through the liver. More recently radioactive iodine has been combined with human serum albumin and in such a state the radioactivity is maintained much longer.[3] The test can be repeated as necessary and the results confirmed. Geiger counters were used in the early work but later the more sensitive scintillation counters came into use.[8] With the scintillation counter an adequate test can be made in about 45 minutes as compared with the two to three hours required for the original technique.

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A number of positron-emitting isotopes such as copper —64, manganese —52, and arsenic —74 have been tried, but only radioactive arsenic is reportedly being given an extensive trial in the localization of brain tumors.[2] Each positron combines with a free electron and mutual annihilation occurs. In this process two gamma rays called annihilation radiation are emitted in opposite directions. Only the annihilation radiation is picked up by the instrument employed. It is thus possible to eliminate scatter, and a relatively stronger radiation is found coming from the tumor where the radioactive material is concentrated.

Selverstone[7] and associates at Harvard first used radioactive phosphorus to define the location of tumors at the time of operation. A Geiger counter in the end of a probe 2 mm. in diameter was passed into the brain and the tumor was detected by the increased counting rates when neoplastic tissue was encountered. Tumors that were difficult to locate by other means could generally be found without undue difficulty.

METHOD AND RESULTS

Use of needle probe. In Chart 1 the experience of the authors in using radioactive phosphorus to determine the location of expanding intracranial lesions at operation is illustrated by six representative cases. This test was used in a total of 14 patients

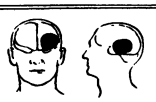
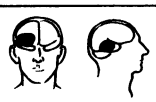
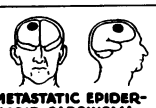
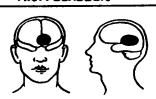
CASE	TUMOR SITE AND TYPE	DIFFERENTIAL COUNT (RADIOACTIVITY of TUMOR / RADIOACTIVITY of BRAIN)	COMMENT
♂ AGE: 51 YRS.	 GANGLIOGLIOMA	8:1	TUMOR LOCATED WITH RADIOISOTOPE NEEDLE THROUGH BURR HOLE. BIOPSY OBTAINED BEFORE BONE FLAP WAS TURNED.
♀ AGE: 45 YRS.	 MALIGNANT GLIOMA	5:1	TUMOR DIFFUSE, NO DIFFERENCE IN TEXTURE NOTED WHEN VENTRICULAR NEEDLE WAS PASSED IN TO BRAIN. WITH RADIOISOTOPE NEEDLE, TUMOR LOCATED, BIOPSY TAKEN.
♂ AGE: 29 YRS.	 ASTROCYTOMA	7:1	TUMOR EXTENDED INTO BASAL GANGLIA. HEMISPHERECTOMY WOULD HAVE BEEN REQUIRED FOR A CURE. RADIOISOTOPE NEEDLE OUTLINED EXTENT of TUMOR.
♂ AGE: 59 YRS.	 GLIOBLASTOMA MULTIFORME	15:1	EXTENT OF CYSTIC TUMOR DETERMINED WITH RADIOISOTOPE NEEDLE. TOO DEEP IN MAJOR HEMISPHERE FOR REMOVAL.
♂ AGE: 69 YRS.	 METASTATIC EPIDERMOID CARCINOMA FROM BLADDER	5:1	TUMOR SMALL, NOT LOCATED UNTIL RADIOISOTOPE NEEDLE WAS USED.
♂ AGE: 39 YRS.	 MALIGNANT ASTROCYTOMA	8.5:1	TUMOR NOT LOCATED UNTIL RADIOISOTOPE NEEDLE WAS USED. SATISFACTORY BIOPSY TAKEN. TUMOR UNRESECTABLE.

Chart 1

and the only failure was in a patient with a brain abscess. In the 14 cases of tumor the neoplasm was found without difficulty. The radioactivity of the most active portion of the cerebral neoplasm was never less than five times the activity of the normal brain. In one case, that of a very vascular meningioma, the radioactivity of the new growth was 60 times that of the surrounding cerebral tissue.

The counter makes a clicking sound that is clearly audible in the operating room and when the sensitive tip of the needle is passed into the tumor the increase in the counting rate is usually obvious. It is only occasionally necessary to wait for the physicist to make a complete count before the location of the tumor is known.

It was often possible to estimate the gross extent of a tumor before the surgical incision was made. At times the lesion was located through a solitary burr hole and some idea of its size gathered by measuring the depths at which increased radioactivity was encountered. In some cases, however, the spread of the tumor was greater than indicated in tests with the needle, as parts of tumors at times gave negative responses.

Five hundred microcuries of radioactive phosphorus were given adults of average size. The material was administered intravenously at intervals that varied from 2 to 3 minutes to 2 hours before the radioactivity was determined. The phosphorus was often not injected until after the operation had commenced and it had become obvious that the lesion would be difficult to find. This method of finding the tumor was used when necessary as an emergency procedure and the level of radioactivity in the tumor was found to be adequate within a few minutes after the injection.

TABLE 1.—*Accuracy of localization of 39 tumors of cerebral hemispheres with radioactive iodine (tagged with albumin or diiodofluorescein) when 10 per cent increase in activity was accepted as "foci"**

	No. Cases
Foci over site of tumor	24
Foci not over site of tumor	6
Foci not present	9

*Foci = point at which radioactivity as measured externally with scintillation counter is greater than in surrounding area or in corresponding area in opposite cerebral hemisphere. (In the data in this table "foci" was point where there was as much as 10 per cent increase in activity.)

External localization. At first, radioactive iodine labelled with diiodofluorescein was used in attempts to localize brain tumors prior to operation. The dosage given was usually 1 millicurie. However, since diiodofluorescein rapidly disappeared from the circulation during the examination, iodine in combination with albumin was used later. In the latter combination the radioactivity is maintained at a useful level for at least 48 hours, and it is possible to repeat the test and establish the validity of the findings.

One hundred and thirty-eight patients who were thought to have intracerebral lesions were tested. Fifty of them had brain tumors that were confirmed by microscopic examination of tissue removed at operation. In 11 cases the tumors were in the posterior fossa or the midline, and were unsuitable for testing by this means. Lesions in the posterior fossa are shielded by heavy muscles and midline lesions give counting rates that are equal on both sides. The remaining 39 neoplasms were in the cerebral hemispheres where they would be nearer the counter.

It was decided that any sustained increase in local radioactivity of 10 per cent or more over that of the surrounding area would be considered significant when 1,024 counts were made. When that standard was used foci of increased radioactivity were found over the tumor in 24 cases (61 per cent of the 39 hemispheral tumors [see Table 1]). Foci were found in areas other than over the tumor in six cases (15 per cent). These false localizations were most common in relatively avascular tumors, e.g., astrocytomas, and it was apparent that the normal brain in

TABLE 2.—*Use of radioisotope test (iodine) as screening test for organic brain disease*

Diagnosis	No. Cases	Focus Found
No organic brain disease	16	1
Cerebral atrophy	23	8
Cerebrovascular accident (any type)	12	10
Brain tumor (any location)	50	34

such instances had picked up more of the radioactive ion. In nine cases (23 per cent) there was no focal increase in radioactivity.

It was obvious that a failure to find a focus of increased radioactivity was of no value in ruling out the presence of a tumor. Additional study was made of those cases of neoplasm in which focal activity was found. Foci of activity were present in 30 of the 39 hemispheral tumors, and in 24 of the 30 the increased radioactivity was over the tumor. Therefore if the negative findings were discarded the focal activity, when present, was over the tumor in 80 per cent of the cases.

There were a number of instances in which the increased radioactivity was much greater than the 10 per cent increase that had been originally determined as being a significant variation and it was thought that in these the findings might be somewhat more reliable. There was no case of false localization in which the local radioactivity was increased by more than 20 per cent. There were 19 cases in which the local cerebral radioactivity was increased by 24 per cent or more, and in all of these the increase was over the site of the tumor. Although there was a high degree of accuracy of localization if only the cases in which the activity was strongly positive were considered, it is unfortunate that such findings were present in slightly less than half the tumors of the cerebral hemispheres that were studied.

The radioisotope test was positive in many diseases other than neoplastic (see Table 2). For example, foci of increased radioactivity were found in 10 of 12 cases of cerebrovascular accident. Foci were also found in 8 of 23 cases of idiopathic adult cerebral atrophy. In 50 brain tumors in all locations in the intracranial cavity, foci were found in 34 (68 per cent). However, a false positive result was found in only one of the 16 cases studied in which no evidence of organic brain disease was found.

GENERAL CONSIDERATIONS

Certain pathologic disturbances in the brain, e.g., tumors, inflammations, vascular diseases, tend to increase the rate of passage of some ions across the so-called "blood-brain barrier." If these ions are made radioactive their presence can be detected by sensitive instruments. In tumors there may be additional factors at work; increased metabolic activity, for example, might cause the phosphorus ion to concentrate.

Peyton and others reported they were able to localize correctly 65 per cent of brain tumors.[6] Ashkenazy and associates claimed an accuracy of 90 per cent in 150 verified space-occupying lesions.[1] Other reports told of varying degrees of success. The difference in results with various groups of patients has been difficult to explain. It seems probable that in only those cases where the tumor is in the lateral portion of the cerebral hemispheres and is of sufficient size, will the test be of value in localizing the lesion. It is usually possible by other means, e.g., ventriculography or angiography, to determine whether or not the tumor is in the cerebral hemispheres. When it has been ascertained that the tumor is in the cerebral hemisphere, the authors believe, the radioisotope test may give important additional information as to the site. It has not been of help in localizing posterior fossa or midline neoplasms. The radioisotope test appears to be of help in screening groups of persons who are suspected of having organic intracerebral disease. It is thought that the findings of a focus of increased radioactivity should arouse a strong suspicion that a neurological lesion is present.

Brain tumors are often difficult to localize at operation even after all available diagnostic means have been used. Selverstone and co-workers demonstrated that radioactive phosphorus injected before or during operation would produce a sufficient increase in radioactivity in the tumor to enable localization with a needle Geiger tube.[7] Morley and Jefferson in England had similar success in 32 cases of brain tumor.[4] At the White Memorial Hospital it was possible to localize 14 out of 15 expanding lesions. The one failure was in a case of abscess.

The authors believe the use of this technique to be a useful adjunct to the other means of locating a tumor at the time of operation. The tumor can often be found more rapidly and with less trauma to the brain. In certain cases it is possible to find the lesion and obtain a specimen for biopsy through a solitary burr hole. If the lesion be highly malignant and deep, major craniotomy can be avoided. The technique in which radioactive phosphorus is used to localize tumors during operation has been found to be very accurate. The method using radioactive iodine-tagged human serum albumin to study the patient before operation has been found to be much less accurate. However, the authors believe this latter procedure deserves a place in the study

of intracerebral tumors as well as other types of brain disease.

At present the accuracy of the results achieved preoperatively is not great enough to allow its use alone in determining the site of the pathological process. However, the presence of a focus of increased activity above 20 per cent in the series of cases studied at the White Memorial Hospital always indicated the correct location of the pathology in cases of tumor.

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Messages to Patients

THE PUBLIC RELATIONS DEPARTMENT of the California Medical Association reported recently that a record total of more than 1,000,000 of the personal physician-to-patient messages have been ordered by the physicians of the state for distribution to their patients and their families.

The messages cover a variety of down-to-earth medical topics and are being made available to C.M.A. members without charge.

Newspapers throughout the state have publicized the profession's desire to make emergency medical care available at all times and the willingness of physicians to discuss matters revolving around the selection of the best prepaid medical care plans and the matter of fees.

This publicizing of the individual physician's sincere desire to be the patient's "health engineer" has also resulted in a number of favorable editorials in important publications.

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California physicians may also take pride in the fact that more than 7,000 doctors in the state—about as many as in all the rest of the 47 states—now display the A.M.A. plaque on fees and services in their offices. The plaque has been termed one of the most fundamental of all public relations tools for physicians.

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